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Journal of Exercise Science & Fitness 10 (2012) 23–27

www.elsevier.com/locate/jesf

Original article

Simple prediction formula for peak oxygen consumption in patients with chronic heart failure

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Received 8 June 2011; revised 19 January 2012; accepted 13 February 2012
Available online 5 June 2012

Abstract

Peak oxygen consumption (VO_2) is one of the strongest predictors of survival in patients with chronic congestive heart failure (CHF), but it is unavailable in most practices. Peak VO_2 < 14 mL/kg/min identifies patients who might benefit from referral to a specialized CHF center. Accordingly, the current study was undertaken to derive a prediction formula based on routine stress data obtained from patients referred for cardiopulmonary exercise tolerance testing (CPETT). Subsequently, the prediction formula was validated in a separate cohort of similar patients referred for CPETT at another institution. The derivation cohort consisted of 208 patients with a diagnosis of CHF with reduced systolic function (left ventricular ejection fraction < 40%) who underwent elective CPETT. A multiple linear regression analysis was performed on available treadmill testing variables. A simple prediction formula was derived: Predicted peak VO_2 = 16.7 − 1.3 (sex) − 3.8 × (New York Heart Association functional class) + 0.04 × (peak heart rate) + 0.92 × (estimated metabolic equivalents). The validation cohort consisted of 112 patients referred for CPETT at a different institution for the evaluation of advanced CHF. The predicted peak VO_2 as obtained by the prediction formula was compared to the actual peak VO_2 using a Pearson coefficient of correlation. The predicted peak VO_2 was well correlated with the actual peak VO_2 demonstrating a correlation coefficient of $r = 0.77$ with a 95% confidence interval of (0.68−0.83). A simple prediction formula using four variables that are routinely obtained in standard exercise treadmill testing can identify patients in whom formal CPETT is advisable and facilitate early referral to specialized heart failure centers.

Keywords: Exercise treadmill test; Heart rate; Metabolic equivalents; Sex

Introduction

Peak oxygen consumption (VO_2) and other variables determined by cardiopulmonary exercise tolerance testing (CPETT) are used to quantify exercise capacity and to demonstrate whether exercise limitation is indeed cardiac in etiology.[1–3] It can be determined by analyzing the concentrations of O_2 and CO_2 in expired air during exercise with rapidly responding gas analyzers capable of breath-by-breath determination of O_2 and CO_2 concentrations.[4] CPETT is one of the principal tests used to assess the risk/benefit ratio of advanced therapies such as orthotopic heart transplantation (OHT) or left ventricular assist device (LVAD) implantation in patients with end-stage chronic congestive heart failure

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doi:10.1016/j.jesf.2012.04.005

(CHF).[5,6] For patients with a peak $VO_2 > 14$ mL/kg/min, 1-year survival was 94%, whereas those patients with peak $VO_2 < 14$ mL/kg/min had a 1-year survival of 70%.[5] Patients with peak $VO_2 < 12$ mL/kg/min treated with β-adrenoceptor blockers have a similar survival profile as patients not treated and a peak $VO_2 < 14$ mL/kg/min.[7] Despite the usefulness of CPETT in the risk stratification of CHF, many tertiary centers that treat patients with CHF do not have the capability of performing CPETT. In contrast, standard exercise treadmill testing (ETT) can be routinely carried out in most cardiology practices.

Although there are multiple peak VO_2 prediction formulas, many of them are complicated or are derived from groups of healthy volunteers. A large study that excluded patients with severe CHF utilized several different formulas to predict peak VO_2, with the main variable being duration of exercise and other variables being sex, weight, age and activity level.[8] Other investigators have either derived or validated different prediction formulas for peak VO_2 obtained during CPETT. Variables that have been commonly used in these formulas include duration of exercise, workload (in metabolic equivalents; METs), perceived workload (Borg scale), peak heart rate (HR), sex, weight, age, activity level, height, and years of exercise training.[9–15] The Wasserman and Hansen formula, which uses age, sex, mode of exercise, sedentary lifestyle, height and weight to calculate a percent-predicted peak VO2,[16] has been well studied and shown to have prognostic significance.[17] However, many of these prediction formulas require inputting several variables, thus, there may be a need for a simpler formula that can easily be done during standard ETT.

Accordingly, the present study was undertaken to identify routine variables obtained during an electrocardiographic exercise tolerance test that could reliably predict peak VO_2. A regression analysis was performed to create a best-fit, simple formula that encompassed four variables: sex, peak HR, peak workload (estimated METs) and New York Heart Association (NYHA) functional class. Subsequently, this prediction formula was validated by applying it to a separate cohort of similar subjects referred for CPETT in the evaluation of advanced CHF.

Methods

This investigation was conducted in two parts. The derivation cohort was studied at one CHF center and the validation cohort was analyzed at a separate CHF center. Both parts of the study were approved by their respective institutional review boards.

Both cohorts were ambulatory patients with systolic CHF [left ventricular ejection fraction (LVEF) < 40%], who were physically capable of performing graded treadmill exercise for a long enough duration to achieve a respiratory exchange ratio (RER) > 1. The RER is the ratio of VCO_2 to VO_2 as measured with the metabolic cart during the exercise protocol. RER > 1.0 was taken as a surrogate for the patients having exerted sufficient effort to stress their cardiovascular system maximally beyond the anaerobic threshold. Many factors may lead to a patient not obtaining an RER > 1.0, including insufficient effort, claudication, musculoskeletal pain or excessive dyspnea related to pulmonary disease. As a result of this exclusion criterion, patients with significant gait impairment or other mechanical disability were not enrolled. Additionally, patients were excluded if they had a left ventricular assist device (LVAD), atrial fibrillation or resting dyspnea (NYHA functional class IV).

The baseline clinical characteristics including background medical therapy of both the derivation and validation cohorts are shown in Table 1. In the derivation cohort, mean age was 51 ± 11 years, mean LVEF was 23 ± 7%, etiology of CHF was ischemic heart disease in 34% of patients, 67% were NYHA functional class III, and 74% were male. In the validation cohort, mean age was 53 ± 9 years, mean LVEF was 23 ± 6%, etiology of CHF was ischemic heart disease in 39% of patients, 55% were NYHA functional class III, and 77% were male.

Derivation cohort

Between January 1, 2002 and June 30, 2003, 558 consecutive patients with a history of CHF were referred for initial CPETT as a part of routine clinical testing or evaluation for OHT. Patients who had undergone bicycle exercise ergometry ($n = 49$), with atrial fibrillation ($n = 38$), with no information on LVEF ($n = 60$), with an unknown NYHA functional class ($n = 47$), had a LVAD ($n = 18$), or failed to achieve an RER > 1.0 ($n = 138$) were excluded. Thus, 208 patients who met the selection criteria for the derivation cohort were analyzed.

Table 1
Baseline clinical characteristics of study patients.

Characteristic	Derivation cohort	Validation cohort
Total patients (*n*)	208	112
Age (yr)	51 ± 11	53 ± 9
Male sex (%)	74	77
LVEF (%)	23 ± 7	23 ± 6
ICM (%)	34	39
NIDCM (%)	66	61
NYHA functional class, %		
I	0	12
II	33	45
III	67	55
Medications (%)		
ACE inhibitors	85	78
ARBs	11	16
β-Blockers	69	92
Spironolactone	23	37
Digoxin	81	77
Diuretics	80	76

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ICM = ischemic cardiomyopathy; LVEF = left ventricular ejection fraction; NIDCM = nonischemic cardiomyopathy; NYHA = New York Heart Association.

Validation cohort

At a separate institution, 317 consecutive patients referred for CPETT were identified from January 1, 2008 until December 30, 2010. Patients were included if they had been referred for the test by a CHF specialist at that center and had a LVEF $< 40\%$. Patients were excluded if they were in atrial fibrillation ($n = 15$), could not achieve a RER > 1.0 ($n = 110$), had a LVAD ($n = 15$), or if the information about their NYHA functional class ($n = 17$) or LVEF ($n = 4$) was not documented in their medical records or if LVEF was $\geq 40\%$ ($n = 44$). Thus, 112 patients who met the selection criteria for the validation cohort were analyzed.

CPETT

Peak VO_2 (mL/kg/min) was assessed during graded treadmill exercise. The work rate increased continuously in a stepwise manner by augmenting the speed and grade of the treadmill according to the Naughton protocol. Patients exercised to a symptom-limited maximum. HR and electrocardiography were recorded continuously during exercise and blood pressure was measured at rest, and every 2 minutes during exercise and during recovery. Expired gases were collected throughout the protocol, and oxygen consumption was calculated on a breath-by-breath basis (Sensormedics, Yorba Linda, CA, USA). Peak VO_2 was defined as the highest value of oxygen uptake attained in the final 20 seconds of exercise when RER was > 1.0.

At the second center where the validation cohort was analyzed, the protocol for CPETT was similar, except the metabolic cart was manufactured by Innovision (Innocor®) (Model # 500; Odense, Denmark) and the patients exercised using a modified Naughton protocol. A similar RER > 1.0 was taken as the cut-off for sufficient exercise during CPETT.

Statistical analysis

Multiple linear regression analysis was carried out to derive the peak VO_2 prediction formula using the data from the derivation cohort. The analysis included 23 demographic and clinical variables: age, sex, etiology of CHF, NYHA functional class, medication use (β-adrenoceptor blocker, antiarrhythmic therapy, digoxin, angiotensin converting enzyme inhibitor, angiotensin receptor blocker, spironolactone, diuretic, and statin), baseline mean arterial pressure (MAP), maximal MAP, exercise time, RER, peak workload (estimated METs), baseline HR, peak HR, peak HR change from baseline, HR at 1 minute post-exercise (HRR1) and HR at 2 minutes post-exercise (HRR2). The backward selection technique was first used to identify the variables significantly associated with peak VO_2 at the 5% level in the multiple linear regression. The resulting model had an effect size (R^2) of 0.85 and included the variables of sex, NYHA functional class, peak workload (estimated METs), peak HR, HRR1 and HRR2. As a result of the high correlations among the HR variables, we decided to include only peak HR, which gave the best prediction in the formula to achieve a more parsimonious model. The final prediction formula was:

$$\begin{aligned}\text{Predicted peak } VO_2 \;=\; & 16.7 - 1.3(\text{sex}) - 3.8 \\ & \times (\text{NYHA functional class}) + 0.04 \\ & \times \text{peak HR} + 0.92 \\ & \times (\text{estimated METs}).\end{aligned}$$

The correlation between peak VO_2 and its prediction was estimated by 0.90. Using this derived prediction formula, the Pearson correlation coefficient was calculated between the predicted peak VO_2 and the actual peak VO_2 in the validation cohort. TJV was provided the variables to calculate the predicted peak VO_2 and was blinded to the actual peak VO_2. A forward step-wise multiple regression model was used to quantify predictors of peak VO_2 using sex, peak HR, NYHA functional class and peak workload (estimated METs) as independent variables. These were chosen because they had strong classifiers of having a low or high peak VO_2. A p value < 0.05 was considered statistically significant. All analyses were conducted using SPSS 13.0 software.

Results

The rest and exercise hemodynamic data are summarized in Table 2. In the derivation cohort, the mean peak VO_2 was 17.5 ± 6 mL/kg/min with 31% of the patients having a peak $VO_2 < 14$ mL/kg/min. The baseline HR was 75 ± 13 bpm with a peak HR of 134 ± 25 bpm. The baseline MAP was 80 ± 13 mmHg and the peak MAP was 91 ± 14 mmHg. In the validation cohort, the mean peak VO_2 was 16.0 ± 5 mL/kg/min with 32% of the patients having a peak $VO_2 < 14$ mL/kg/min. The baseline HR was 71 ± 11 bpm, peak HR was 118 ± 20 bpm, baseline MAP was 85 ± 12 mmHg and peak MAP was 91 ± 16 mmHg.

Using the simple formula to predict the peak VO_2 obtained by patients in the validation cohort, there was a moderate and statistically significant correlation coefficient of 0.77 ($p < 0.0001$) with a 95% confidence interval of (0.68–0.83) (Fig. 1).

Using a forward step-wise regression model to predict peak VO_2, peak HR explained the greatest percentage of variance in peak VO_2 (31%), followed by NYHA functional class (30%), peak estimated METs (14%) and sex (5%) ($p < 0.001$ for model, Table 3). The multiple R from the regression equation was 0.89 and R^2 was 0.80.

Table 2
Rest and exercise hemodynamics of study patients.

	Derivation cohort	Validation cohort
Peak VO_2 (mL/kg/min)	17.5 ± 6	16.0 ± 5
Baseline HR (bpm)	75 ± 13	71 ± 11
Peak HR (bpm)	134 ± 25	118 ± 20
Baseline MAP (mmHg)	80 ± 13	85 ± 12
Peak MAP (mmHg)	91 ± 14	91 ± 16

HR = heart rate; MAP = mean arterial pressure; VO_2 = oxygen consumption.

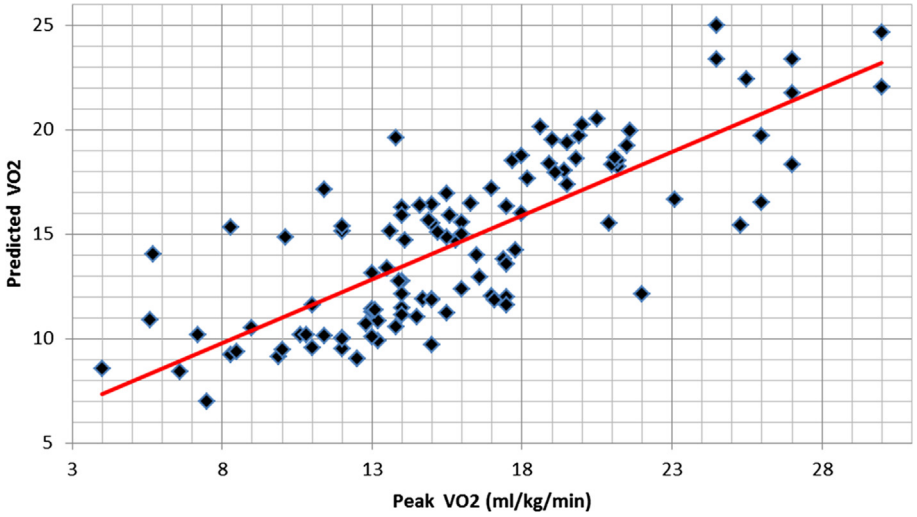

Fig. 1. Scatter plot with best-fit trend line. $R = 0.77$ (confidence interval 0.68–0.83; $p < 0.0001$).

Discussion

A prediction formula for peak VO_2 was created based on 208 patients with CHF referred for CPETT and subsequently validated in 112 patients with similar baseline clinical characteristics. The variables of peak HR, estimated METs, NYHA functional class and sex were highly significant in predicting peak VO_2. If this formula can be validated in prospective studies, then centers that do not have a metabolic cart and trained personnel required to perform CPETT would have an additional tool for the selection of patients that would benefit from early referral to centers for formal CPETT and OHT or LVAD evaluation.

Separately, the factors in this proposed formula for predicting peak VO_2 have been shown to correlate with the actual peak VO_2. In an analysis of 1750 patients in the HF-ACTION database, NYHA functional class II corresponded to a peak VO_2 of 16.1 ± 4.6 mL/kg/min versus 13.0 ± 4.2 mL/kg/min in patients that were NYHA functional class III.[17] Maximal HR achieved is preserved in patients with a healthy response to exercise, and has been shown to correlate with peak VO2.[18] In CHF, it has been shown that 30–50% of patients cannot achieve 80% of their maximal predicted HR, and are thus chronotropically incompetent. In one analysis of 278 patients undergoing CPETT, chronotropic incompetence correlated with a decreased peak VO_2 (average 15.4 mL/kg/min) and mean decreased peak HR (114 bpm) as compared to CHF patients devoid of chronotropic incompetence, who had a mean peak VO_2 of 19.9 mL/kg/min and mean peak HR of 152 bpm.[19] Male patients are associated with a consistently higher peak VO_2 (about 1.6 mL/kg/min) than female patients, regardless of NYHA functional class.[20,21] Finally, decreased workload has also been shown to be prognostic of 1-year mortality and correlates with peak VO_2 in patients with CHF.[9,22]

Table 3
Correlation matrix between clinical, demographic and exercise variables.

Variable	R	R^2	Added variance explained (%)	p value
Sex	0.22	0.05	5	0.002
Peak HR	0.60	0.36	31	< 0.001
NYHA functional class	0.81	0.66	30	< 0.001
Peak estimated METs	0.89	0.80	14	< 0.001

HR = heart rate; METs = metabolic equivalents; NYHA = New York Heart Association.

Although blinded to the actual variables, our study was mainly limited by the fact that the validation cohort was analyzed retrospectively. The exercise protocol in the derivation cohort was a Naughton protocol, whereas in the validation cohort, it was a modified Naughton protocol. This is unlikely to have affected the results of the correlation found with the prediction formula because both groups exercised to a symptom-limited maximum. Additionally, it has been shown that the peak VO_2 obtained during CPETT is similar between different exercise protocols.[23] Another limitation of this prediction formula is that it is unlikely to predict accurately peak VO_2 in patients without CHF or patients with symptomatic CHF and preserved systolic function. The latter group of patients has an equivalent mortality to CHF patients with reduced systolic function.[24]

A theoretical limitation of this formula is the potential that the relationship between peak VO_2 and the exercise treadmill variables used is not linear. In the original prediction formulas derived by Bruce et al,[9] there are different formulas for treadmill performance (submaximal or maximal effort), sedentary lifestyle and cardiac status, with the result being a nonlinear model using multiple formulas It is possible that the correlation of this formula in the present study was preserved because patients were excluded if they did not achieve an anaerobic threshold or RER > 1.0. The only way to test whether this simple prediction formula can predict peak VO_2 in patients with a submaximal CPETT is to test it prospectively in all patients, regardless of RER obtained, which may be difficult because there are many non-

cardiopulmonary factors that can limit a patient's ability to exercise on a treadmill protocol.

Taken together, these four variables that are easily obtainable during a routine stress test in a practitioner's office could potentially allow the estimation of a patient's peak VO_2, and signal the need for referral for further evaluation at a center with advanced CHF capabilities. This simple formula for predicting peak VO_2 cannot replace a CPETT, but if further validated in prospective studies, could offer another tool for the general cardiologist in the management of patients with CHF. Additionally, if this prediction formula is again validated on a larger scale, it could potentially be incorporated into risk stratification models like the Heart Failure Survival Score, further enhancing its prognostic potential.

In conclusion, the current study proposes a formula for predicting peak VO_2 based on variables that are easily obtained from routine ETT. If validated by prospective studies, it offers an additional, low-cost tool for the risk-stratification and management of patients with CHF.

References

1. Hunt SA, Abraham WT, Chin MH, et al. Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation. *J Am Coll Cardiol*. 2009;53:e1−e90.
2. Taylor DO, Edwards LB, Aurora P, et al. Registry of the International Society for Heart and Lung Transplantation: twenty-fifth official adult heart transplant report—2008. *J Heart Lung Transplant*. 2008;27:943−956.
3. Weber KT, Janicki JS. Cardiopulmonary exercise testing for evaluation of chronic cardiac failure. *Am J Cardiol*. 1985;55:22A−31A.
4. Neuberg GW, Friedman SH, Weiss MB, et al. Cardiopulmonary exercise testing. The clinical value of gas exchange data. *Arch Intern Med*. 1988;148:2221−2226.
5. Mancini DM, Eisen H, Kussmaul W, et al. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation*. 1991;83:778−786.
6. Mancini DM. Cardiopulmonary exercise testing for heart transplant candidate selection. *Cardiologia*. 1997;42:579−584.
7. Mancini D, LeJemtel T, Aaronson K. Peak VO(2): a simple yet enduring standard. *Circulation*. 2000;101:1080−1082.
8. Bruce RA, Kusumi F, Hosmer D. Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. *Am Heart J*. 1973;85:546−562.
9. Chandrashekhar Y, Anand IS. Can common exercise indices determine peak exercise oxygen consumption and anaerobic threshold during stress testing in patients with chronic congestive heart failure? *Indian Heart J*. 1993;45:493−495.
10. Davis JA, Storer TW, Caiozzo VJ, et al. Lower reference limit for maximal oxygen uptake in men and women. *Clin Physiol Funct Imaging*. 2002;22:332−338.
11. Eston R, Lambrick D, Sheppard K, et al. Prediction of maximal oxygen uptake in sedentary males from a perceptually regulated, sub-maximal graded exercise test. *J Sports Sci*. 2008;26:131−139.
12. Foster C, Jackson AS, Pollock ML, et al. Generalized equations for predicting functional capacity from treadmill performance. *Am Heart J*. 1984;107:1229−1234.
13. Hansen JE, Sue DY, Wasserman K. Predicted values for clinical exercise testing. *Am Rev Respir Dis*. 1984;129:S49−S55.
14. Malek MH, Housh TJ, Berger DE, et al. A new nonexercise-based VO2(max) equation for aerobically trained females. *Med Sci Sports Exerc*. 2004;36:1804−1810.
15. Storer TW, Davis JA, Caiozzo VJ. Accurate prediction of VO2max in cycle ergometry. *Med Sci Sports Exerc*. 1990;22:704−712.
16. Wasserman K. *Principles of Exercise Testing and Interpretation: Including Pathophysiology and Clinical Applications*. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2005.
17. Arena R, Myers J, Abella J, et al. Determining the preferred percent-predicted equation for peak oxygen consumption in patients with heart failure. *Circ Heart Fail*. 2009;2:113−120.
18. Russell SD, Saval MA, Robbins JL, et al. New York Heart Association functional class predicts exercise parameters in the current era. *Am Heart J*. 2009;158(4 Suppl.):S24−S30.
19. Fairbairn MS, Blackie SP, McElvaney NG, et al. Prediction of heart rate and oxygen uptake during incremental and maximal exercise in healthy adults. *Chest*. 1994;105:1365−1369.
20. Jorde UP, Vittorio TJ, Kasper ME, et al. Chronotropic incompetence, beta-blockers, and functional capacity in advanced congestive heart failure: time to pace? *Eur J Heart Fail*. 2008;10:96−101.
21. Pina IL, Kokkinos P, Kao A, et al. Baseline differences in the HF-ACTION trial by sex. *Am Heart J*. 2009;158(4 Suppl.):S16−S23.
22. Huelsmann M, Stefenelli T, Berger R, et al. Prognostic impact of workload in patients with congestive heart failure. *Am Heart J*. 2002;143:308−312.
23. Strzelczyk TA, Cusick DA, Pfeifer PB, et al. Value of the Bruce protocol to determine peak exercise oxygen consumption in patients evaluated for cardiac transplantation. *Am Heart J*. 2001;142:466−475.
24. Chen HH, Lainchbury JG, Senni M, et al. Diastolic heart failure in the community: clinical profile, natural history, therapy, and impact of proposed diagnostic criteria. *J Card Fail*. 2002;8:279−287.